International Preliminary Examination Authority
The European Patent Office
Erhardtstraße 27
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Germany

1 February 2006

Dear Sirs

International Patent Application No. PCT/GB2005/001451
ATHERA BIOTECHNOLOGIES AB
Our Ref: ATHCZ/P32969PC

This is a response to the Written Opinion of the International Searching Authority dated 11 August 2005. It is to be noted that a Demand for International Preliminary Examination was filed on 13 December 2005, but that this response is filed within the time limit set down by the communication PCT/ISA/237 from the International Searching Authority, pursuant to Rule 66.1 PCT.

We enclose an amended claim set, in which Claims 6, 7 and 9 have been deleted. Previous Claim 8 has been split into new Claims 6 and 7. Previous Claims 10 and 11 have been re-numbered accordingly. Further, new Claim 9 has been amended to read "*A method according to Claim 8, or a use according to Claim 6 or Claim 7,...*" to render it also dependent on new Claims 6 and 7 (previous Claim 8). Basis for this amendment may be found at *inter alia* page 6, line 13 to page 7, line 7.

We also enclose an annotated version of the previous claim set for convenience.

In the first instance, we refer the examiner to *inter alia* page 16, lines 9 to 19 of the application as filed and the experiments described therein, upon which the claimed invention is based. The claimed invention stems from an unexpected observation by the applicant that:

(a) Annexin V is present in atherosclerotic lesions at many sites, especially those that are prone to plaque rupture; and

(b) a decrease in Annexin V binding, for example as a consequence of interference by antibodies, increases the risk of atherothrombosis and/or plaque rupture.

Therefore, restoring Annexin V binding provides a possible novel therapy for atherothrombosis and particularly plaque rupture, which is the main cause of

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cardovascular disease. This may be achieved by either:

(i) the use of the Annexin V protein itself, or an N-terminal fragment of Annexin V, to enhance binding (Claims 1 to 5; see point 1 below); or

(ii) the use of an immunoglobulin with the capacity to inhibit antibodies binding to Annexin V, and/or to promote binding of the latter to the endothelium (new Claims 6 to 8; previous Claims 6, 10 and 11; see point 3 below).

We shall now deal with the examiner's objections in turn.

1. The examiner has objected to Claims 1 to 5, alleging that Claims 1 to 4 lack novelty over documents D1, D2 and D4 and/or that Claims 1 to 5 lack inventive step over documents D1, D2 and D4 in the light of document D3 and/or D7.

Document D1 relies on the use of Annexin V as an agent that localises at a lesion within a blood vessel or other body lumen (see first sentence at paragraph [0036] of D1). The inventors in D1 have utilised the affinity of stressed or apoptotic cells for exogenously administered Annexin V to create a multi-functional molecular probe that may be used in therapy. This probe consists of (with reference to paragraphs [0028] and [0029], as well as Claim 1, of D1):

(a) Annexin V to promote ***binding***;

(b) a radioisotope, such as technetium-99m, which permits localisation of the composition at the site of interest; and

(c) an effecter molecule which selectively kills or inhibits the stressed or apoptotic cells. This effecter molecule is typically a light-absorbing porphyrin which, when sensitised by light, selectively destroys the damaged tissue.

In other words, the multi-functional molecular probe of D1 is a three-component system, comprising Annexin V as a binding molecule. The probe is used to selectively destroy cells by light sensitisation. There is absolutely no disclosure or suggestion in D1 that the Annexin V protein or an N-terminal fragment thereof would be useful in the prevention of atherosclerotic plaque rupture.

Claims 1 to 4 are accordingly novel and inventive over document D1.

In relation to D2, this document discloses a modified Annexin, which comprises a recombinant human Annexin protein coupled to a polyethylene glycol, which is then used in the treatment of arterial or venous ***thrombosis*** (i.e. blood clots). The use of such a modified Annexin in atherosclerotic conditions is in no way suggested by D2. The use of the Annexin V protein itself, or an N-terminal

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fragment thereof, in the prevention of atherosclerotic plaque rupture is certainly not suggested. D2 is therefore completely irrelevant to the patentability of Claims 1 to 5 as is document D4, which also relates to arterial thrombosis.

Document D3, is an abstract published by the same group that published the patent application that is document D1. D3 describes very briefly a study designed to determine whether Annexin V reduces apoptotic activity in atherosclerotic plaques. Apparently (although this is not clear), the results show a decrease in apoptotic activity. At best, therefore, the results of D3 show that Annexin V may reduce apoptotic activity in atherosclerotic plaques. However, this is not the same thing as prevention of plaque rupture. Treatment of atherosclerosis (i.e. the prevention of plaque ***growth***) does not necessarily lead to prevention of plaque rupture, as these are to all intents and purposes separate biological processes. It is known, for example, that estrogen may be used to treat atherosclerosis but cannot be used to prevent plaque rupture (see, for example, Wagner and Clarkson *Semin. Reprod. Med.* (2005), **23**, 149; copy enclosed).

Thus, Claims 1 to 4, and any claims that depend on or from them (i.e. Claim 5) are novel and inventive over cited prior art documents D1, D2 and D4, alone or in combination with D3. There is no suggestion in any of these documents that the Annexin V protein or a N-terminal fragment thereof may be used in the prevention of plaque rupture (and therefore atherothrombosis) in a patient at risk of the latter.

2. The examiner has objected to Claims 6, 7 and 9 in the light of document D8.

Whilst we do not agree with the examiner's conclusions, our deletion of the relevant claims renders this objection moot.

3. The examiner alleges that previous Claims 8 and 10 (now Claims 6, 7 and 8) lack novelty over documents D5 and D6.

First of all, there is no suggestion in either of the relevant documents of the use of purified subfractions of pooled immunoglobulins with the capacity to either inhibit antibodies binding to Annexin V, and/or promote the binding of Annexin V to endothelium, in the prevention of plaque rupture.

This notwithstanding, document D5 relates to the use of the commercially available pooled immunoglobulin preparation, IVIG, in the treatment of heart

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disorders. However, paragraph [0023] suggests that the coronary syndromes that are to be treated include "*unstable and angina pectoris, non-Q wave myocardial infarction and Q-wave myocardial infarction*". It is then stated that "*These syndromes are believed to be the common pathophysiological substrate caused by a rupture of an atherosclerotic plaque in one of the coronary arteries*".

Hence it is clear that the relevant disclosure in D5 does not relate to the prevention of plaque rupture ***as such***, but rather just conditions that may ***result*** from e.g. plaque rupture.

D6, on the other hand, appears to relate to the use of IVIG in the prevention of atherosclerosis as such. As discussed at point 1 above, prevention of atherosclerotic growth is not the same thing as the prevention of plaque rupture, but rather the formation of the plaques themselves.

In this regard, documents D5 and D6 are irrelevant to the patentability of Claims 6, 7 and 8.

In relation to the examiner's comments regarding industrial applicability and under Item VIII of the Written Opinion, we believe that these do not require further comment at this stage and will be better dealt with during national prosecution.

None of the enclosed amendments add subject matter. Any amendment is not to be construed as abandonment of subject matter.

We look forward to the receipt of a favourable International Preliminary Report on Patentability (Chapter II). However, should the examiner not be inclined to agree with these observations, we should appreciate the opportunity to make further representations, either by way of a telephone discussion or a further written response prior to the issuance of the relevant report.

Yours faithfully

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Stephen McNeeney PhD
For and on behalf of Eric Potter Clarkson LLP

Enc: amended claims (re-typed and annotated)
Wagner and Clarkson, *Semin. Reprod. Med.* (2005) **23**, 149